

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

(Attorney Docket No. SIR-MIS-00001-US-CIP[4])

IN THE APPLICATION OF:)		
)		
McSwiggen <i>et al.</i>)		
)		
Serial No.: 10/757,803)	Examiner:	BOWMAN, Amy
)		Hudson
Filed: January 14, 2004)	Group Art Unit:	1635
)		
)		
Title RNA Interference Mediated)	Confirmation No.:	5421
Inhibition of Gene Expression)		
Using Chemically Modified)		
Short Interfering Nucleic Acid)		
(siNA))		

REPLY BRIEF UNDER 37 C.F.R. §41.41

Peter Haeberli
Attorney for Applicant
Merck & Co., Inc.
1700 Owens Street, 4th Floor
San Francisco, CA 94158
Phone: (415) 814-8491
Fax: (415) 512-7022

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

(Attorney Docket No. SIR-MIS-00001-US-CIP[4])

IN THE APPLICATION OF:)		
)		
McSwiggen <i>et al.</i>)		
)		
Serial No.: 10/757,803)	Examiner:	BOWMAN, Amy
)		Hudson
Filed: January 14, 2004)	Group Art Unit:	1635
)		
)		
Title RNA Interference Mediated)	Confirmation No.:	5421
Inhibition of Gene Expression)		
Using Chemically Modified)		
Short Interfering Nucleic Acid)		
(siNA))		

REPLY BRIEF UNDER 37 C.F.R. §41.41

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is filed in response to the Examiner's Answer mailed on May 3, 2011. No fee is thought to be presently due, but the Commissioner is authorized to charge payment of any additional fees required in connection with the paper(s) transmitted herewith, or to credit any overpayment of the same, to Deposit Account No. 50-4615.

Contents

Real Party in Interest.....	4
Related Appeals and Interferences.....	4
Status of Claims.....	4
Status of Amendments.....	4
Summary of the Claimed Subject Matter.....	4
Grounds of Rejection to be Reviewed on Appeal.....	7
Argument.....	8
Conclusions.....	26
Appendix A: Claims on Appeal	
Appendix B: Evidence	
Appendix C: Related Proceedings	
Appendix D: Amendments in the Claims	

REAL PARTY IN INTEREST

The real party in interest is Sirna Therapeutics Inc., a wholly owned subsidiary of Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828). A copy of the Board's decision is attached as Appendix C.

Appeal No. 2011-006291, resulting from application 10/720,448, currently pending before the board.

STATUS OF CLAIMS

A Final Office Action was mailed on October 21, 2010. Claims 18-20 and 33-49 stand rejected and are presently pending. Claims 1-17 and 21-32 were previously canceled. The rejections of claims 18-20 and 33-49 are appealed with this submission. A copy of the claims on appeal is attached in Appendix A.

STATUS OF AMENDMENTS

No claims are amended.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention provides certain chemically modified short interfering nucleic acid molecules having a sense strand and an antisense strand that mediate RNA interference. Each strand of the claimed nucleic acid molecules is between 18 and 24 nucleotides in length. The sense strand includes a terminal cap moiety at its 5' and 3' ends and the antisense strand includes a terminal cap moiety at its 3' end. Furthermore, 10 or more pyrimidine nucleotides of the sense strand and/or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. *See* claims 18 and 40; Specification at, *inter alia*, page 30, lines 2-7; and page 83, lines 5-7. *See* additionally Figures 18 and 19; Table I (beginning at page 227) and Table IV (page 239) for numerous examples of the presently claimed chemically modified nucleic acid

molecules.

Each strand of the chemically modified short interfering nucleic acid molecules described above can be further modified with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages. *See* claims 39 and 48; Specification at, *inter alia*, page 30, lines 5-6; Figures 18 and 19; Table I (beginning at page 227) and Table IV (page 239).

The chemically modified short interfering nucleic acid molecules can have one or more ribonucleotides (claims 20 and 42) or alternately can comprise no ribonucleotides (claims 19 and 41). *See* specification at, *inter alia*, page 14, lines 14-16.

One or more of the pyrimidine nucleotides in the sense strand of the chemically modified short interfering nucleic acid molecule can be a 2'-O-methyl pyrimidine nucleotide. *See* claims 33 and 43; Specification at, *inter alia*, page 30, lines 2-4; Figures 18 and 19 (A, B, C); Table I (beginning at page 227) and Table IV (page 239) *e.g.*, "Stab 6" and "Stab 17".

One or more of the purine nucleotides in the sense strand of the chemically modified short interfering nucleic acid molecule can be a 2'-deoxy purine nucleotide. *See* claims 34 and 44; Specification at, *inter alia*, page 38, lines 7-10; Figures 18 and 19 (D, F); Table I (beginning at page 227) and Table IV (page 239) *e.g.*, "Stab 7".

One or more of the pyrimidine nucleotides in the sense and/or antisense strand of the chemically modified short interfering nucleic acid molecule can be a 2'-deoxy-2'-fluoro pyrimidine nucleotide. *See* claims 35, 36, 45 and 46; Specification at, *inter alia*, page 30, lines 2-4; Figures 18 and 19 (A, B, C, D, E, F); Table I (beginning at page 227) and Table IV (page 239) *e.g.*, "Stab 3", "Stab 4", "Stab 5", "Stab 7", "Stab 8", "Stab 11", "Stab 12", "Stab 13", "Stab 14", and "Stab 18".

One or more of the purine nucleotides in the antisense strand of the chemically modified short interfering nucleic acid molecule can be a 2'-O-methyl purine nucleotide. *See* claims 37 and 47; Specification at, *inter alia*, page 39, lines 18-21; Figures 18 and 19

(D, E); Table I (beginning at page 227) and Table IV (page 239) *e.g.*, "Stab 8", and "Stab 19".

The present invention also pertains to a composition comprising one of the molecules depicted above in a pharmaceutically acceptable carrier or diluent. *See* claims 38 and 49; Specification at, *inter alia*, page 19, lines 30-31.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The issue on appeal is:

- (I) Whether claims 18-20 and 33-49 are obvious under 35 U.S.C. § 103(a) over Elbashir et al. (EMBO J., 2001, 20(23):6877) in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, 2000, 6:1077-87), and Crooke (US 5,898,031).

ARGUMENT

I. Claims 18-20 and 33-49 are inventive and not obvious

In response to the Examiner's Answer mailed May 3, 2011, and as set forth in the Appeal Brief filed March 14, 2011, Applicant maintains that the present invention is clearly inventive and non-obvious. The pioneering discovery of RNA interference (RNAi) by Fire and Mello (see US Patent No. 6,506,559) provided a revolutionary new approach to inhibit the expression of any given gene. This discovery was recognized by the 2006 Nobel Prize in physiology or medicine. Nevertheless, as is often the case with pioneering discoveries in medicine, additional sequential innovation was required to advance the technology from the laboratory to the clinic. Indeed, the later discovery of short interfering RNA (siRNA) by Tuschl, Zamore, Sharp, and Bartel (see US Application No. 20020086356, "Tuschl I") identified the molecular triggers of the RNAi mechanism. Subsequent work by Tuschl, Elbashir, and Lendeckel (see US Application No. 20040229266, "Tuschl II") sought to further characterize and optimize the RNAi triggers. The results of this characterization and optimization were summarized in a "The siRNA User Guide," (see US Application No. 20040229266, page 49; see also Elbashir et al., EMBO J., 2001, 20(23):6885) which provided the state of the art siRNA molecules at the time of the instant invention.

These state of the art siRNA molecules were stabilized with 2'-deoxy modification of the 3'-terminal overhang regions of the duplex. Specifically, "2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes" (see Elbashir, EMBO J., 2001, 20(23): 6885). Attempts at more extensive modification, i.e., beyond the 3'-termini, was taught to "*reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly*" (Id). When tested by Applicant, the state of the art siRNA taught by Elbashir having modified 3'-terminal overhangs demonstrated a half life in human serum of only 15 seconds. While such molecules may be useful as a research tool *in vitro*, they would not have utility as part of a therapeutic regimen. On the other hand, extensively modified siRNA

molecules of the instant invention, having 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modified pyrimidine nucleotides of the sense strand and/or antisense strand and having 3' and 5'-terminal cap modification of the sense strand and 3'-terminal cap modification of the antisense strand, have demonstrated serum half lives of up to 40 days (*see* Figure 3 of the instant application; *see* also Figure 3 of the earliest priority document recognized by the Office, USSN 60/408,378 filed September 5, 2002; *see* also Figure 3 of USSN 60/358,580 filed February 20, 2002 to which Applicant has previously asserted priority and which shows an increase in serum half life from 15 seconds to 72 hours). Furthermore, these extensively modified siRNA molecules show surprisingly robust RNAi activity that is equivalent or even improved compared to the state of the art at the time of filing (*see* **Figures 3, 14, 15, 28, 29, and 30** and discussion thereof *infra* at page 20).

The present invention has significantly advanced the state of the art by providing synthetic siRNA molecules that are extensively modified yet which surprisingly maintain robust or improved RNA interference activity, thus enabling the use of such molecules as therapeutic modalities. The Office maintains that this significant advancement over the prior art resulted merely from "routine optimization," and alleges that the invention is *prima facie* obvious. Specifically, claims 18-20 and 33-49 remain rejected under 35 U.S.C. 103(a) as allegedly being obvious in view of Elbashir (EMBO J., 2001, 20(23):6877), Matulic-Adamic (US 5,998,203), Parrish (Molecular Cell, 2000, 6:1077-87), and Crooke (US 5,898,031). *See* Examiner's Answer, page 5. Applicant respectfully traverses and relies upon well established jurisprudence, as discussed below, to prove otherwise.

Applicant maintains that the presently claimed invention cannot be obvious for at least three reasons as set forth in the Appeal Brief filed March 14, 2011. First, one of skill in the art would *not have had any reasonable expectation of success* in practicing the claimed invention because the prior art either taught away from the claimed invention or indicated a high level of unpredictability that would have precluded any reasonable expectation of success. Second, it is impermissible hindsight to conclude that the present invention is obvious because it would have been "obvious to try" using combinations of

known modifications via "routine optimization," especially since the prior art gave “no direction as to which of many possible choices is likely to be successful” and offered “only general guidance as to the particular form of the claimed invention or how to achieve it.” *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Finally, even if a *prima facie* finding of obviousness could be established, the *failure of others*, along with the *surprising results* obtained in practicing the invention, serve to effectively rebut any such presumption of obviousness.

1. No reasonable expectation of success

The Office alleges (*see* Examiner's Answer, page 19):

There would have certainly been a reasonable expectation of activity within the instantly claimed genus of molecules given the motivation to routinely optimize siRNA molecules via balancing stability and activity wherein the molecules are readily tested and screened via routine techniques in the art. One would reasonably expect that routine optimization via adding modifications to test for stability and preservation of half life would result in active molecules when utilizing modifications that are routinely utilized to enhance the activity of nucleic acid inhibitory molecules.

Applicant respectfully traverses and maintains that one of skill in the art at the time of the invention would not have any reasonable expectation of success in practicing the claimed invention because of the teaching away and high level of unpredictability provided by the cited art with respect to the ability of extensively modified siRNA to mediate RNA interference. MPEP § 2143.03(VI) states that “[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” A reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Here, because the Elbashir reference discloses problems with respect to more extensive modification beyond the 3'-terminal portions of a siRNA, and because these teachings are based on the proposed RNAi mechanism as it was understood at the time of the invention, one of skill in the art would not be inclined to extensively modify siRNA molecules nor have any reasonable expectation of success in doing so. As such, the teachings of Elbashir et al., as a whole, teach away from the instantly claimed invention that requires significant modification beyond the 3'-terminal overhang portions of a siRNA duplex.

The Office, acknowledges that "Elbashir et al. teaches 19% successful modification and teaches that 50% or 100% (one or both full strands) with 2'-deoxy or 2'-O-methyl (one modification only) abolished activity." Examiner's Answer, page 12. Yet, the Office maintains that "[t]he fact that Elbashir et al. is silent as to modification between 19% and 100% (of one or both strands) would in fact motivate the skilled artisan to modify more extensively than the 19% to optimize the activity/stability balance." Examiner's Answer, page 15. On the contrary, Applicant maintains that at the time of the invention, Elbashir et al. as a whole effectively taught away from one of skill in the art making and using active siRNA duplexes that are more extensively modified than the 19% level of modification that was shown to maintain RNAi activity (only up to four 2'-deoxy modifications at the 3'-terminus of each strand were shown to be tolerated). This is because of the author's specific teachings relating to their discussion of the impact of modification beyond the 3'-terminus on the RNA interference mechanism of action, specifically the ability of the more extensively modified siRNA to associate with the protein complex required for RNAi.

Elbashir *et al.* described siRNA duplexes having from 9.5% to 100% of the nucleotides modified in each strand by replacing the 2'-hydroxyl group of said nucleotides with either 2'-deoxy or 2'-O-methyl. Figure 4 shows that when the two, overhanging 3' nucleotides of each strand were modified (representing 9.5% of duplex nucleotides) with 2'-deoxy nucleotides, RNAi activity was maintained. The same result was found when the two additional nucleotides adjacent to the 3' overhangs of each strand were modified (representing 19% of the duplex nucleotides). However, when either one strand of the duplex was modified (representing 50% of the duplex nucleotides) or both strands of the duplex were modified (representing 100% of the duplex nucleotides), RNAi activity was abolished. The authors summarize their findings in the Discussion section of the paper under the heading "The siRNA user guide" providing specific guidance to those skilled in the art for generating siRNA duplexes that are more palatable from a manufacturing cost perspective, and which may have enhanced resistance to nuclease degradation. The authors state on page 6885, with emphasis added, the following:

*Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and **must** be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

It should be noted that the teachings of the Elbashir reference have been reviewed by the BPAI (see attached decision, Appendix C) who found that "[a] fair reading of [Elbashir]...is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi." Appeal 2009-002562, at page 27. This fair reading is consistent with the position that extensive modification and, in particular, modification beyond the 3'-terminal regions of one or both strands of a siRNA molecule, is either expressly taught away from, or in the alternative, is highly unpredictable in view of the teachings of Elbashir et al., especially since their conclusions were premised on mechanistic incompatibility, i.e., that more extensive modifications interfere with protein association for siRNP assembly.

The Office's position completely ignores the Elbashir et al. author's discussion of the impact of modification beyond the 3'-overhangs on the RNAi mechanism. Citing *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009), the Office recognized in the Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex (Notices) that, "[a]n inference that a claimed combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." Fed. Reg. 75:169 (September 1, 2010) page 53649. Clearly, one of skill in the art, having read the teachings of Elbashir et al., who warn against more extensive modification beyond the 3'-terminal regions due to proposed mechanistic concerns over the ability of the siRNA to associate with proteins required for RNAi, and who explicitly show that modification of ~50-100% of the nucleotide positions of the siRNA duplex abolished RNAi activity, would certainly not have any reasonable expectation of success in arriving at active molecules that are extensively modified well beyond the 3'-terminal overhang regions as is clearly required by subparts (c) and (d) of independent claims 18 and 40.

The Office on the other hand alleges that the Board's interpretation of "The siRNA user guide" is consistent with the position that the Elbashir reference only teaches away from 100% modification with 2'-deoxy or 2'-O-methyl because "[s]tating that complete substitution abolished RNAi is not the same of [*sic*] stating that any 2'-O-methyl modification should be avoided." Examiner's Answer, page 13. The Office appears to confuse the issue before the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858) with the issue currently at hand. The claims reviewed in the related appeal only required a single 2'-O-methyl modification in addition to a single 2'-deoxy-2'-fluoro modification, i.e., only two modifications in total and which could be concentrated in the 3'-overhang of each strand. In comparison, the instant claims require a terminal cap at both 3' and 5' ends of the sense strand and the 3'-end of the antisense strand, and in addition, 10 or more pyrimidine nucleotides of the sense and antisense strand (Claim 18), or the sense or antisense strand (Claim 40) are modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro. Thus, Applicant's arguments do not rest on a teaching away premised on "any" 2'-O-methyl modification which could be limited to two nucleotides of the terminal 3'-overhang regions, but rather a teaching away premised on more extensive modification that would necessarily require a significant impact well beyond any terminal 3'-overhang portions in each strand of the siRNA duplex.

The Office incorrectly asserts that "[t]he minimum required by the instant claims in fact is not far off from what was exemplified to work by Elbashir et al., given that the instant modifications can be concentrated in the terminal regions." Examiner's Answer, page 15. The Office also incorrectly asserts that "Therefore, the deminimus of the instant claims is 5 modifications per strand, one single modification more than the successful exemplification of Elbashir et al. Even when incorporating 10 modifications per strand out of a possible 24 nucleotides, some level of activity would be expected, especially if the modifications are concentrated in the terminal regions" Examiner's Answer, page 16. Applicant respectfully submits that these statements are in error. First, Elbashir et al. did not show successful modification of the "terminal regions", as this would necessarily include both the 3' and the 5'-ends of each strand. Second, the current claims require modification of not only the 3' and 5'-ends of the sense strand and the 3'-end of the antisense strand, but also modification of 10 or more pyrimidine nucleotides of the sense

and antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro (Claim 18) or modification of 10 or more pyrimidine nucleotides of the sense or antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro (Claim 40). It is therefore difficult to imagine how the instantly claimed requirements would be concentrated only at the 3'-terminal regions as taught by Elbashir et al. The Office's assertion that "[t]he minimum required by the instant claims in fact is not far off from what was exemplified to work by Elbashir et al., given that the instant modifications can be concentrated in the terminal regions" simply cannot stand. The fact remains that there is a clear teaching away in Elbashir et al. from modifications that extend beyond the 3'-terminal regions of the siRNA duplex, and that the authors discussion of incompatibility of more extensive modification with protein association required for RNAi renders such modification beyond the 3'-terminal regions highly unpredictable so as to preclude any reasonable expectation of success.

There is nothing in Parrish et al. to remedy the deficiencies of Elbashir et al., especially the strong teaching away with respect to modification of siRNA beyond the 3'-overhangs. Regarding Parrish, the Office asserts that "Parrish teaches extensive 2'-deoxy-2'-fluoro uridine modification with strong RNAi activity. The 2'-deoxy-2'-fluoro uridine modifications represents a dsRNA that was extensively modified and acted via RNAi. There is no reason to expect that shorter dsRNAs, wherein Parrish itself teaches that duplexes 26bp in length act via RNAi, would not remain active with the same modifications, particularly given that the long dsRNA of Parrish was necessarily cleaved via Dicer in the cell into short siRNA molecules in order to be loaded into RISC and be active." Examiner's Answer, page 19.

Applicant maintains that the teachings of Parrish et al., especially in view of the Elbashir author's discussion thereof, provide an additional level of unpredictability so as to preclude any reasonable expectation of success with respect to the modified short interfering nucleic acid molecules as presently claimed. First, contrary to the Office's assertion, one of skill in the art at the time of the invention would not expect the long 2'-deoxy-2'-fluoro modified dsRNA of Parrish et al. to be cleaved into siRNA by Dicer, as this would be contrary to the intent of using chemical modifications in the first place (to

preclude any enzymatic cleavage activity). And even if 2'-deoxy-2'-fluoro modifications in long dsRNA were shown to be processed by Dicer, then one of skill in the art certainly would not be motivated to incorporate such modification into siRNA to improve nuclease resistance. Furthermore, Parrish observed that the 26 bp dsRNA required a 250-fold higher concentration requirement than the longer dsRNA for interference activity (see page 1078), which would further steer one of skill in the art away from modification of short RNA duplexes. More importantly, Parrish demonstrated that chemical modifications, when introduced into long dsRNAs, produce highly unpredictable results. Elbashir et al. specifically addressed the Parrish et al. findings and provided detailed commentary on these unpredictable results with respect to their own observations on the deleterious effects of more extensive modification in the siRNA duplex, i.e. modifications extending beyond the 3'-terminus (see Elbashir et al., page 6886).

The functional anatomy of long dsRNAs as a trigger for RNAi was analysed previously in C.elegans (Parrish et al., 2000). Activation of RNAi by injection of long dsRNA requires at least two steps: dsRNA processing by dicer RNase III and siRNP or RISC formation. Substitution of one of the strands of the long dsRNA by DNA abolished RNAi and even the substitution of C by dC or U by dT in only one of the strands caused a substantial decrease in RNAi. Because introduction of 2'-fluoro modifications into long RNA had no effect, it was suggested that an A-form double helical structure was important for triggering RNAi (Parrish et al., 2000). We have been able to substitute eight ribose residues of a siRNA duplex by 2'-deoxyribose residues without substantial reduction of RNAi, although it should be noted the 2'-deoxy modifications were clustered at the 3' end of the siRNAs, including the 2 nt 3' overhangs. It is possible that the four 2'-deoxy modifications, which are located in the paired region at the end of the helix, do not affect the overall A-form helical structure and do not strongly compromise RISC formation. Complete modification of one or both siRNA strands by 2'-deoxyribose, however, abolished RNAi. Interestingly, substitution by 2'-O-methylribose, which adopts the ribose sugar pucker, also abolished RNAi, probably because methylation of the 2'-hydroxyls blocked hydrogen bond formation or introduced steric hindrance.

The above discussion, which addresses mechanistic concerns of modification beyond the 3'-overhang regions and the *unpredictable effects of such modification*, coupled with the plain language of "The siRNA user guide," which states that more extensive modification with 2'-deoxy and 2'-O-methyl beyond the 3'-overhangs results in reduced RNAi activity "probably by interfering with protein association for siRNP assembly," provides a strong teaching away and a high level of unpredictability with

respect to more extensive modification of siRNA beyond the 3'-overhangs. Furthermore, any predictability based on known modification specific criteria (i.e., based on the long dsRNA, ribozyme, or antisense arts), such as the ability to form an A-form helix, are destroyed by the lack of RNAi activity observed with 2'-O-methyl modifications. Parrish et al., which only provides one example of successful modification in *long* (742 base pair) RNA duplexes, but several examples of unsuccessful modification, does nothing to remedy the lack of predictability and ultimate teaching away provided by Elbashir with respect to *short* interfering RNA duplexes as instantly claimed. Taken together, the Elbashir and Parrish references provide a strong teaching away from, and such a high level of unpredictability, so as to preclude one of skill in the art (as demonstrated by the authors themselves) from arriving at or practicing the instantly claimed invention.

As discussed in the Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex (Notices), "[a] claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results." Fed. Reg. 75:169 (September 1, 2010) page 53647 (citing *Crocs, Inc. v. U.S. Int'l Trade Comm'n.*, 598 F.3d 1294 (Fed. Cir. 2010)). The combination of features presently claimed, in view of the cited art that teaches against extensive modification of siRNA due to mechanistic concerns, ***would not yield a predictable result and, accordingly, one of skill in the art at the time of the invention would not have any reasonable expectation of success.*** Therefore, Applicant maintains that the Examiner's assertion that the instant invention is the result of "routine optimization" (Examiner's Answer, page 10 citing *In re Aller*, 105 USPQ 233 at 235) is clearly erroneous and ignores the teachings away and unpredictability of the cited art with respect to extensive modification of siRNA that was evident at the time of the instant invention.

In conclusion, Applicant agrees with the BPAI's characterization of the closest prior art in stating that "[a] fair reading of [Elbashir]...is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi." Appeal 2009-002562, at page 27. There is nothing in Matulic-Adamic or Crooke, which teach modification strategies unique to ribozymes and

antisense respectively, to remedy the shortcomings or teaching away that is evident in both Elbashir and Parrish. Because the instant invention requires terminal cap modifications on both the 3' and 5'-ends of the sense strand and the 3'-end of the antisense strand, *in addition to* 10 or more modified pyrimidines (2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro) in the sense strand and/or antisense strand, in view of the teachings of Elbashir et al., one of skill in the art at the time of the instant invention would simply not have any reasonable expectation of success due to the strong lack of predictability with respect to the ability of these molecules to mediate RNAi.

2. "Obvious to try" analysis fails to find obviousness

The Office alleges that the Applicant's view of Elbashir is in error "given that reduction in the ability to mediate RNAi still yields molecules that are active" and that "[i]t is widely accepted in the nucleic acid inhibitor field that a balance is needed between stability and activity and thus a reduction in activity is often accepted to gain stability, as long as the molecule is still active." Examiner's Answer, page 15. The Office concludes that "[o]ne would reasonably expect that routine optimization via adding modifications to test for stability and preservation of half life would result in active molecules when utilizing modifications that are routinely utilized to enhance the activity of nucleic acid inhibitory molecules" Examiner's Answer, page 19. With these conclusions, Applicant maintains that the Office appears to rely on hindsight in putting forth the proposition that sooner or later one of skill in the art would arrive at the instant invention by simply testing various combinations of modifications and locations. This hindsight analysis clearly ignores the teaching away and high level of unpredictability that was evident at the time of the instant invention, as evidenced in the fact that the Office's statements above are premised in the present tense, i.e., what is presently known, as opposed to the past tense, i.e. what was known at the time of the instant invention. Furthermore, at the time of the invention, the state of the art Elbashir et al. reference did not teach that reduction in the ability to mediate RNAi still yields molecules that are active, but rather characterized their findings as either "without loss of activity", or in the alternative "abolished RNAi" (Elbashir et al., page 6882).

The Office is essentially arguing that the present invention would be "obvious to try" by using known modifications and routine experimentation and is therefore *prima facie* obvious. Applicant respectfully traverses. As recognized by the Office and as discussed in the Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex* (Notices), Fed. Reg. 75:169 (September 1, 2010) page 53653, the Federal Circuit has clarified the standard for a finding of obviousness based on an "obvious to try" inquiry in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). Specifically, while acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.*, a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, the Federal Circuit held that it would be improper to hold a claim obvious when:

What would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

What was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009)

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" inquiry to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell*, at 903-04 and Fed. Reg. 75:169 (September 1, 2010) pages 53653-4. On the contrary, the combined teachings of the references cited against the pending claims do not provide guidance as to what individual modifications, when used "more extensively," will result in siRNA molecules that are both active and stable. In fact, the combined teachings actually indicate that more

extensive incorporation of modifications into siRNA is detrimental and/or at least highly unpredictable based on the proposed mechanism of action, i.e. *by interfering with protein association for siRNP assembly*. The prior art references, therefore, provide no guidance or any level of predictability that would lead one of skill in the art to conclude there was a reasonable expectation of success in combining the features presently claimed. Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness.

A reading of the cited prior art reveals a vast number of possible modifications that were available to one of skill in the art at the time of the instant invention. The Office, in hindsight, attempts to oversimplify the criteria as being limited to only two choices, i.e. modification of purine vs. pyrimidine nucleotides, when stating that "there are only two options to incorporate the instant modifications, purine or pyrimidines; wherein the quantity and location of purines or pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target." Examiner's Answer, page 21. Applicant respectfully traverses this oversimplification of the invention, as the claims do not simply specify purine vs. pyrimidine modifications, but rather require selections from at least *3 different criteria*: (1) the types of modifications, i.e. 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, (2) the positions of certain modifications, i.e. terminal caps at both the 3' and 5'-ends of the sense strand and the 3'-end of the antisense strand; and, (3) the type of nucleotide that is modified irrespective of its position within the duplex, i.e. 10 or more pyrimidine nucleotides. Therefore, the present invention could not have possibly arisen from routine optimization.

Even if one takes the position that routine testing with known modifications and known assays would *eventually* lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fail to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications when applied more extensively. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to the types of modifications one could apply to a siRNA molecule, providing merely a large selection of possibilities to choose from.

These known modifications were individually demonstrated by those who first studied short dsRNA in the field to be sometimes feasible with limited application, but more often than not were incompatible with RNAi activity due mechanistic concerns, i.e., incompatibility with the siRNP protein machinery that is required to mediate RNAi. That unpredictability grows only larger if the known modifications were applied more extensively, and in combination, as is presently claimed. Thus, although numerous types of modifications were known in the art, this was not a case of testing a finite number of identified, predictable solutions. ***"In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."*** *Kubin*, at 1359.

Therefore, this is not an instance where the prior art contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, ***and evidence suggesting that it would be successful***. Rather, it is an instance where the prior art provides no direction as to which of many possible choices is likely to be successful and only general guidance as to the particular form of the claimed invention or how to achieve it. Most importantly (as addressed previously), the prior art, by teaching away from (or at least rendering highly unpredictable) more extensive modification beyond the 3'-termini, evidenced such a high level of unpredictability to preclude any reasonable expectation of success in practicing the claimed invention. Applicant's arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell*.

3. Secondary indicia preclude any finding of obviousness

Applicant maintains that no *prima facie* finding of obviousness can stand in view of the lack of motivation or any reasonable expectation of success that is evident from a plain reading of the cited art, and that even an "obvious to try" analysis fails because of the lack of guidance and/or predictability offered by the prior art. However, even if a *prima facie* showing of obviousness could be established, such a finding is effectively

rebutted due to secondary considerations. As recognized by the Office, and as discussed in the Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex* (Notices),"[a]ll evidence, including evidence rebutting a prima facie case of obviousness, must be considered when properly presented." Fed. Reg. 75:169 (September 1, 2010) page 53657 (citing *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007)). It is also well established that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Secondary considerations include the failure of others and unexpected results. MPEP 716.01(a). Specifically, (1) the failure of others, coupled with (2) the surprising results obtained using the instant invention, are a clear and irrefutable demonstration of non-obviousness with respect to the presently claimed invention.

The instant invention provides double stranded nucleic acid molecules that are both highly serum stable and potent in mediating RNA interference, both *in vitro* and *in vivo*. The closest prior art is the Elbashir reference cited herein. It is important to recognize that the authors of Elbashir et al., armed with all of the knowledge proffered by the prior art with respect to chemical modification of nucleic acids (including the previous work published in the Parrish reference that was cited by and commented on by the authors of Elbashir et al., along with the prior teachings of Matulic-Adamic and Crooke), conducted extensive characterization and analysis of double stranded nucleic acid molecules with respect to optimized activity but *failed* in providing molecules that are both serum stable and active (see discussion *supra* and in more detail below with respect to **Figure 3** of the instant application and priority applications). Importantly, Elbashir et al. concluded that more extensive modifications beyond the 3'-termini were not favorable because of mechanistic concerns over the inability of such more extensively modified siRNA to interact with the RNAi protein machinery.

The instant invention is a departure from the teachings of Elbashir's '*The siRNA user guide*' and provides double stranded nucleic acid molecules having features that impart a high level of serum stability yet maintain significant, or even improved, RNAi activity compared to those of the prior art (see **Figures 3, 10, 11, 12, 13, 14, 15, 26, 29,**

30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87 and **Table I and IV** of the instant application, specific examples of which are described in greater detail below). These features are presently claimed, i.e. terminal caps at both the 3' and 5'-ends of the sense strand and the 3'-end of the antisense strand; in addition to 10 or more pyrimidine nucleotides of the sense and/or antisense strand being modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications.

The Office asserts that "[t]he instant claims are not directed to any specific pattern of modification that yielded an unexpected property, but rather are directed to a very broad scope of possible modifications at varying positions depending on the target sequence, given that the claims are not directed to any specific target." Examiner's Answer, page 14. Applicant respectfully disagrees with this highly conclusory characterization of the invention and maintains that the invention, when properly understood, is directed to a specific modification schematic that can be applied to any double stranded nucleic acid sequence as described in the specification, and which consistently provides unexpected results. For example, application of the features of claims 18 or 40 to any duplex sequence will result in a specific structure with well defined features that include: (1) the length of each strand; (2) modification with terminal cap moieties at both the 3' and 5'-ends of the sense strand and the 3'-end of the antisense strand; (3) the modification of 10 or more pyrimidine nucleotides of the sense *and* antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 18) or 10 or more pyrimidine nucleotides of the sense *or* antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 40). Application of these features results in short interfering nucleic acid molecules having high serum stability coupled with a high level of activity/potency. These surprising and unexpected properties are described below with respect to numerous representative examples as shown in the instant application as filed.

Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986). For example, inspection of **Figure 3** of the instant application shows a direct comparison of the state of the art at the time of the invention (modified Elbashir duplex, *see* Figure 4 on

page 6882 of Elbashir *et al.*) to duplexes of the instant invention in terms of nuclease stability. The Elbashir duplex, having 3'-terminal 2'-deoxy modifications (SEQ ID NOs: 394 and 395), when tested in human serum, has a half life ($T_{1/2}$) of *15 seconds*. The duplexes of the instant invention however, all having the features claimed, i.e., 3' and 5'-sense strand and 3'-antisense strand terminal cap(s) with 10 or more of the enumerated pyrimidine modifications in the sense and/or antisense strand, all show dramatically improved nuclease stability: $T_{1/2}$ of *138 minutes* for SEQ ID NOs: 396 and 397; $T_{1/2}$ of *3.7 days* for SEQ ID NOs: 396 and 398; $T_{1/2}$ of *72 minutes* for SEQ ID NOs: 396 and 399; $T_{1/2}$ of *40 days* for SEQ ID NOs: 396 and 400; and $T_{1/2}$ of *32 days* for SEQ ID NOs: 396 and 401.

The Office alleges that "[a]pplicant is pointing to species that are not representative of the instant genus and do not represent unexpected results for the instant genus". Examiner's Answer, page 17. In response, Applicant asserts that the numerous examples of sequences incorporating the claimed features that show surprising and unexpected results are sufficient to accurately represent the scope of the claims. The RNAi activity of numerous representative examples of short interfering nucleic acid duplexes having 3' and 5' sense strand caps, 3' antisense strand caps, and 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications in the sense and/or antisense strand, have *comparable to or even improved RNAi activity* when compared to a representative control duplex of the prior art. See for example **Figure 14**, in which the siGL2 control (Elbashir duplex) is compared to various duplexes of the invention having a "Stab 6" (see Table IV) sense strand (sequence 30222, SEQ ID NO: 373) consisting of 3' and 5'-sense strand and 3'-antisense strand terminal caps with 2'-O-methyl and 2'-deoxy pyrimidine modifications and various "Stab 5" (Table IV) antisense strands, all having 2'-deoxy-2'-fluoro and 2'-deoxy pyrimidine modifications (sequence 30546, SEQ ID NO: 386; sequence 30224, SEQ ID NO: 374; sequence 30551, SEQ ID NO: 387; sequence 30557, SEQ ID NO: 388, and sequence 30558, SEQ ID NO: 389). Also, see for example **Figure 15**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 4", "Stab 8" or "Stab 7" (Table IV) sense strand (sequence 30063, SEQ ID NO: 372; sequence 30434, SEQ ID NO: 384; and sequence 30435, SEQ ID NO: 385 respectively) all consisting of 3' and 5'-sense strand and 3'-

antisense strand caps with 2'-deoxy, 2'-deoxy-2'-fluoro or 2'-O-methyl pyrimidine modifications and a "Stab 8" (Table IV) antisense strand having 2'-deoxy-2'-fluoro pyrimidine and phosphorothioate modifications (sequence 30430, SEQ ID NO: 375). As shown in these figures, the activity of the serum stable double stranded nucleic acid molecules of the invention is an *unexpected finding* in view of the teachings of the closest prior art.

The Office alleges (*see* Examiner's Answer, pages 21-22)

Applicant argues that the instantly claimed compounds have demonstrated unexpected results. However, the data relied upon is not commensurate in scope with the instantly claimed genus, given that the instant claims embrace a huge genus resulting from many possible combinations of types of modifications at a very large genus of possible positions depending on the specific target sequences. Elbashir et al. concentrated on the terminal regions of the siRNA duplex and simply offers motivation to test for incorporation of modifications at other positions. Simply setting forth a duplex that yielded better results does not mean that the instant genus has an unexpected property.

Applicant respectfully traverses. First, as demonstrated above, Elbashir did not concentrate on the "terminal regions" of the siRNA duplex, only the 3'-terminal region was shown to tolerate modification, and only with 2'-deoxy nucleotides. Second, the teaching away and lack of predictability with respect to the RNAi mechanism being able to tolerate modification beyond the 3'-terminal regions would not provide motivation to test for incorporation of modifications at other positions. Finally, Applicant has shown surprising and unexpected results of numerous representative examples (such as described above in **Figures 3, 14 and 15**) of different modified sequences that are representative of the claimed genus, not just one example. There are literally hundreds of specific examples disclosed in the instant application as filed that are representative of the genus as instantly claimed.

The unexpected results, i.e. highly stable siRNA molecules that have unexpectedly robust RNAi activity (contrary to the teaching of the prior art) are also clearly exemplified in additional representative examples in **Figures 28, 29, and 30**. These figures show RNAi activity of various duplexes of the invention (Stab 4/5; Stab 7/8, and Stab 7/11 respectively, all having sense strands with 3' and 5'-terminal caps and antisense strands with 3'-terminal caps, combined with 2'-deoxy and 2'-deoxy-2'-fluoro

pyrimidine modifications with ribonucleotide (Stab 4, Table IV) or 2'-deoxy (Stab 7, Table IV) purines and antisense strands having 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with phosphorothioate modifications and with ribonucleotide (Stab 5, Table IV), 2'-O-methyl (Stab 8, Table IV) or 2'-deoxy (Stab 11, Table IV) purines). These modified short nucleic acid molecules of the invention are compared to an all RNA duplex control in inhibiting HBV gene expression in a dose response time course study (note, all sequences for the constructs in **Figures 28, 29, and 30** are described in **Table I**). As shown in **Figures 28, 29, and 30**, the extensively modified duplexes of the invention all show comparable activity to the all RNA control at day 3, and *improved* activity at day 6 and day 9 time points.

As is clearly shown in these numerous representative examples in **Figures 3, 14, 15, 28, 29, and 30** (amongst others), *the double stranded nucleic acid molecules of the invention are significantly more stable than the double stranded nucleic acid molecules of the prior art, and surprisingly have retained or improved activity over the prior art molecules that allow these molecules to function as therapeutic modalities.* (Emphasis added) Applicant reiterates that a claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results. *Crocs, Inc. v. U.S. Int'l Trade Comm'n.*, 598 F.3d 1294 (Fed. Cir. 2010) The chemically modified short interfering nucleic acid molecules of the instant invention are a significant and inventive advancement over the teachings of the closest prior art Elbashir reference. Elbashir teaches that "more extensive" modification beyond the 3'-termini is detrimental to RNAi activity on mechanistic grounds because of impaired association with the RNAi protein machinery, and that attempts to more extensively modify such molecules resulted in *abolished* RNAi activity. Thus, even if the Office were able to make a *prima facie* showing of obviousness (which is not the case), the failure of others combined with the surprising, unpredictable, and unexpected results as taught by the application as filed and the priority documents, unequivocally preclude any finding of obviousness.

II. Conclusions

The instant claims are patentable. Applicant therefore respectfully requests withdrawal of the standing rejections and allowance of the claims.

Respectfully submitted,

Date: June 30, 2011

By: /Peter Haeberli/

Peter Haeberli
Reg. No. 52,980
Attorney for Applicant

APPENDIX A

CLAIMS ON APPEAL

1. - 17. (Canceled)

18. (Previously presented) A chemically modified double stranded short interfering nucleic acid molecule that mediates RNA interference, wherein:

a) the double stranded nucleic acid comprises a sense strand and an antisense strand;

b) each strand is independently 18 to 24 nucleotides in length;

c) the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end; and

d) 10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides.

19. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein said double stranded nucleic acid molecule comprises no ribonucleotides.

20. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein said double stranded nucleic acid molecule comprises one or more ribonucleotides.

21. - 32. (Canceled)

33. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein one or more pyrimidine nucleotides present in the sense strand are 2'-O-methyl pyrimidine nucleotides.

34. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein one or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides.

35. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein one or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

36. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein one or more pyrimidine nucleotides present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

37. (Previously presented) The double stranded nucleic acid molecule of claim 18, wherein one or more purine nucleotides present in said antisense strand are 2'-O-methyl purine nucleotides.

38. (Previously presented) A composition comprising the double stranded nucleic acid molecule of claim 18 and a pharmaceutically acceptable carrier or diluent.

39. (Previously presented) The double stranded nucleic acid molecule of claim 18, comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages.

40. (Previously presented) A chemically modified double stranded short interfering nucleic acid molecule that mediates RNA interference, wherein:

a) the double stranded nucleic acid comprises a sense strand and an antisense strand;

b) each strand is independently 18 to 24 nucleotides in length;

c) the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end; and

- d) 10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides.
41. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein said double stranded nucleic acid molecule comprises no ribonucleotides.
42. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein said double stranded nucleic acid molecule comprises one or more ribonucleotides.
43. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein one or more pyrimidine nucleotides present in the sense strand are 2'-O-methyl pyrimidine nucleotides.
44. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein one or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides.
45. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein one or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
46. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein one or more pyrimidine nucleotides present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
47. (Previously presented) The double stranded nucleic acid molecule of claim 40, wherein one or more purine nucleotides present in said antisense strand are 2'-O-methyl purine nucleotides.
48. (Previously presented) The double stranded nucleic acid molecule of claim 40, comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages.

49. (Previously presented) A composition comprising the double stranded nucleic acid molecule of claim 40 and a pharmaceutically acceptable carrier or diluent.

APPENDIX B

EVIDENCE APPENDIX

None

APPENDIX C

RELATED PROCEEDINGS APPENDIX

See attached decision for Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).

APPENDIX D

AMENDMENTS IN THE CLAIMS

None